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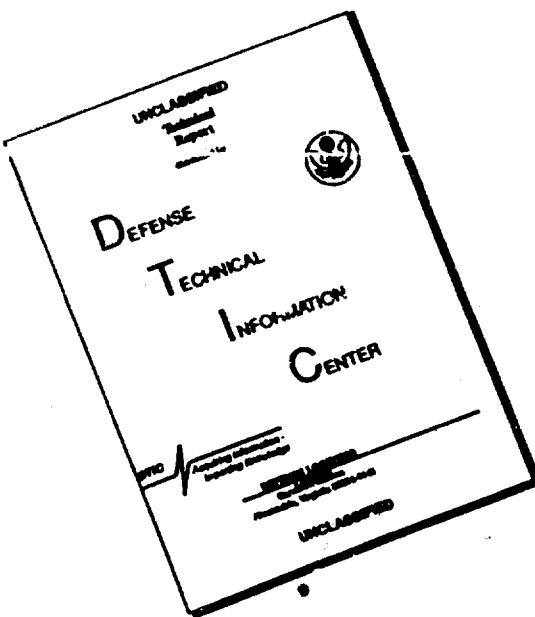
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THE PROBLEM OF ACTIVE IMMUNIZATION WITH COMBINED VACCINES*

THE arsenal of effective measures for the specific prophylaxis of a number of infectious diseases now contains a large number of bacterial and virus preparations, the nomenclature of which increases from year to year. The use of these preparations in anti-epidemic practice, involving the relevant number of injections and the defined intervals between different types of immunization, is now presenting some insurmountable difficulties. This fact has actuated a large number of scientific workers to devote an ever-increasing volume of work to combined vaccines.

A preliminary review of the work carried out in this direction was made at a scientific conference called by the Chief Administration of the Institute of Vaccines and Sera of the Ministry of Health of the U.S.S.R., held in Moscow on 10-11 April 1958. The participants in the conference—representatives from Institutes of Vaccines and Sera and Institutes of Epidemiology, Microbiology and Hygiene—heard and discussed 29 papers, many of which were of great interest.

In his outstanding paper "The Position of Research on the Problem of Combined Vaccines", the Chief Administrator of the Institutes of Vaccine and Sera, A. N. Meshalov, giving a history of the development of the idea of combined vaccines and describing the future investigation to be carried out in this direction, emphasized particularly the groundlessness of the concept of so-called immunological competition (more precisely, incompatibility) of antigens, a concept which has for a long time acted as a brake on the development of combined vaccination. According to the latest scientific findings, the immunological cancellation of one antigen by another on simultaneous injection is of limited importance if the proportions of the antigens in the combination satisfy certain requirements. The possibility and convenience of each combination of antigens, especially when they differ in an immunological respect, must be theoretically grounded and checked by biological experiments taking into account the characteristics of the infective agents against which the active immunization is intended, the pathogenesis of these infections and immunogenesis they provoke. The speaker also stressed that new possibilities in the production of combined vaccines had recently been discovered as a result of the development of rational methods of preparing chemically purified and concentrated antigens which can be included in the vaccine in adsorbed and depot forms.

One of the questions on the programme of the conference was that of the development of a combined preparation against enteric infection and tetanus, the prototype of which is the multiple vaccine produced at NIISI.

Eleven papers devoted to questions of the improvement of the technology of the preparation of this product and of its separate components were given by workers of the Mechnikov Institute of Vaccines and Sera, Moscow, the Gamaleia Institute of Epidemiology and Microbiology, Academy of Medical Sciences of the U.S.S.R., the Leningrad Institute of Vaccines and Sera and the Gor'kov Institute of Epidemiology and Hygiene.

Improvement in the quality of the multiple vaccine was achieved primarily by choosing highly immunogenic strains of the original bacteria, especially *Salmonella paratyphi A*, *Shigella flexneri* and *Vibrio comma*. However, in spite of the definite

progress made in the preparation of combined vaccines against *Salm. paratyphi A*, to the strains of *Sh. flexneri* and *Vib. comma* in combined vaccines, the multiple and co-work of the multiplicity of forms for the Chertkova antigen.

In the Mechnikov Institute of the enteric infections, the use of bacterial and virus antigens, and of the antigenic components, and of the production of combined vaccines.

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Hence, the NIISI type, a logical test of the Mechnikov Institute carried out in Moscow showed, how during the first findings on the prototype of the multiple vaccine, the number of a single immunization was stable and the idea of a 2 doses.

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* Zh. mikrobiol., epidemiol., immunobiol. No. 11, 151-153, 1958.

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progress made in this direction, the selection of highly immunogenic strains of *Salm. paratyphi* A is not yet complete and needs further study. The same applies to the strains of *V. comma* (V. M. Lavrovskaya and others). Some valuable findings on the discovery of a labile antigen of particular significance in immunogenesis in *Sh. flexneri* were reported by V. A. Krestovnikova and co-workers. The inclusion in combined vaccines of the purified Vi antigens from *Escherichia coli*, *Paracolobactrum* and *Salm. typhosa*, increasing the antigenicity of the typhoid fraction of the multiple vaccine, is also of undoubted importance, as shown by V. D. Gekker and co-workers. With regard to the inclusion of tetanus antigen in the composition of the multiple vaccine, the conference agreed unanimously that the most effective form for this component is purified adsorbed toxoid (N. S. Kashintseva, F. A. Cherkova and others).

In the Mechnikov Institute, Moscow, complete antigens from cultures of bacteria of the entero-typhoid group have for many years been obtained from tryptic digests of bacterial colonies. The Gamaleia Institute gave their results on the preparation of the antigens by a water-phenol method. Each of these methods has its advantages, and further observations are needed to provide a final estimation of the productional and immunoprophylactic advantages of the preparations.

A multiple vaccine is an adsorbed preparation, and it is therefore very important to use the adsorbent giving the most complete fixation of the antigenic components and producing the least reaction. E. A. Petrosian and co-workers, who have studied the adsorbing powers of aluminium phosphate, aluminium hydroxide and calcium phosphate, concluded that aluminium hydroxide is the best of these adsorbents.

Hence, the modern multiple vaccine is in many ways different from the old NIISI type, and is a much improved preparation. An epidemiological and immunological test of one of the variations of the improved NIISI multiple vaccines from the Mechnikov Institute of Vaccines and Sera, Moscow (multiple vaccine No. 2) carried out in 1956-57 and involving 16,419 persons (A. B. Kheifets and co-workers) showed, however, that the effectiveness of the preparation was only moderate during the first 6 months and low at later periods after a single inoculation. These findings on the temporary degree of immunity produced after a single inoculation, and the experimental observations of Gorokhovnikova, who studied the significance of the number of inoculations on immunization with multiple vaccine, show that a single immunization, even with remote (after 1 year) revaccination, cannot ensure a stable and sufficiently strong immunity, which means that, without abandoning the idea of a single inoculation, we must at present recommend immunization with 2 doses.

In anti-epidemic practice, corpuscular vaccines are being used and will continue to be used for some time as well as chemical vaccines, and for this reason the question of combined corpuscular vaccines and their perfection is also important. It was the subject of 3 papers given at the conference (A. V. Ponomarev and co-workers, N. G. Klineva and co-workers, I. G. Vasil'eva). Results were described which indicated the superiority of acetone and alcohol vaccines, in which the Vi antigen is preserved. Freeze-drying of the preparations was recommended in order to stabilize their immunizing activity. It was shown at the Leningrad Institute of Vaccines and Sera that of the components of a combined vaccine including typhoid, paratyphoid, dysentery and cholera antigens the *Salm. paratyphi* A and *Sh. sonnei* components were only weakly immunogenic.

Questions of immunization with combined toxoids and also with toxoids combined with a multiple vaccine formed the subject of 7 very interesting papers.

At the Gamaleia Institute (G. V. Vygodchikov and others) a detailed experimental study was made of a purified and adsorbed triple toxoid (*Clostridium tetani* and 2 of the organisms causing gas gangrene, *Cl. perfringens* and *Cl. oedematiens*), and also of a pentatoxoid (the same components, plus *Cl. botulinum* toxoids), in combination with a chemical multiple vaccine against enteric infections. At the Leningrad Institute of Vaccines and Sera (A. V. Poromarev and others) a similar multiple antigen preparation was studied, taking the form of a tetratoxoid (*Cl. tetani* and 3 gas gangrene organisms—*Cl. perfringens*, *Cl. oedematiens* and *Cl. septicum*) in combination with a pentavaccine against enteric infections, prepared from complete bacterial antigens. These combined vaccines against wound and enteric infections had a marked immunological effect. This offers good prospects for their use in case of necessity.

A. N. Ugleva and co-workers, of the Leningrad Institute of Vaccines and Sera, studied a tetravaccine against tetanus and gas gangrene organisms and showed the effectiveness of double immunization with the preparation with an interval of 30 days. After the second inoculation the blood antitoxin titres rose $4\frac{1}{2}$ – $8\frac{1}{2}$ times higher than after a single inoculation.

Some precise, well-documented results of a test of purified concentrated, aluminium hydroxide adsorbed double toxoid of *Cl. perfringens* and *Cl. oedematiens* in 98 volunteers were given in a paper by G. P. Cherkas (Khar'kov Institute of Vaccines and Sera). After 3 doses of this preparation of 0.5, 1 and 1 ml with intervals of 21 days and 90 days the inoculated persons showed high antitoxin titres (up to 4–6 units for *Cl. perfringens* and 5.5–8 units for *Cl. oedematiens*), increasing still further after late revaccination (up to 8 and 15 units respectively). Serum from immunized persons had a good protective effect in white mice affected by gas gangrene.

B. G. Trukhmanov (Tomsk Institute of Vaccines and Sera) showed the theoretical possibility of immunization with a preparation containing 13 or more components of different nature and origin, which he called "multi-antigenic".

Much interest was aroused among the delegates at the conference by a paper by N. P. Efimova and co-workers, of the Perm' Institute of Vaccines and Sera, who succeeded in preparing a polyvalent gas gangrene antiserum on a production scale by immunizing horses with combined depot antigens consisting of *Cl. perfringens*, *Cl. oedematiens* and *Cl. septicum* toxoids.

The last portion of the work of the conference was devoted to the very important question of live combined vaccines, discussed here for the first time. The components of the latter were vaccine preparations of brucellosis, tularemia, plague and anthrax bacilli.

The results of an experimental study in animals and of limited human experiments (E. A. Gubina and others, B. P. Uzbekova, M. F. Shmuter and others) with a combined brucellosis and tularemia vaccine, which on dermal scarification showed a benign inoculation reaction and gave rise to a satisfactory immune response, show that there are good prospects for the practical application of this type of combined vaccine and that there is a basis for carrying out more extensive vaccination experiments with it in foci of infection with brucellosis and tularemia.

E. I. Klets and co-workers, of the Irkutsk Anti-plague Institute, obtained completely satisfactory results in their experiments on the estimation of the reactions and immunological changes in animals during a study of a combined plague, tularemia and brucellosis vaccine, which is evidence of the complete compatibility of its components.

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An attempt at simultaneous inoculation of an STI anthrax vaccine and a live brucellosis vaccine gave unsatisfactory results in an experiment carried out by V. S. Antadze and co-workers (Tiflis Institute of Vaccines and Sera), as did combined vaccination against anthrax, tularaemia and brucellosis in an experiment carried out by N. D. Anina-Radchenko (Odessa Institute of Epidemiology and Microbiology). The anthrax component in this form of combined vaccination inhibited immunogenesis, i.e. it was incompatible with the other antigens in the vaccine.

Such are the main features of the first stage in the study of combined vaccination with bacterial and toxoid preparations. A number of valuable suggestions arising from the papers given at the conference call for more precision in the production of the preparations (a limited number of components, in the correct dosage) and schedules for their use in practice.

Unfortunately, no papers on the combined use of virus preparations were given at the conference except for 1 paper (by S. A. Ananian and G. I. Medvedeva) on the compatibility of the components of a combined live vaccine against yellow fever, sandfly fever and smallpox.

The development of combined virus, virus-rickettsial and virus-bacterial vaccines, together with further work on the problem of bacterial and toxoid combined vaccines, should be considered the next problem facing microbiologists, virologists and epidemiologists.

B. G. VAINBERG
Translated by J. J. OLIVER